

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 July 2000 (18.07.00)	
International application No. PCT/EP99/09053	Applicant's or agent's file reference 0/98414 WO
International filing date (day/month/year) 18 November 1999 (18.11.99)	Priority date (day/month/year) 20 November 1998 (20.11.98)
Applicant LOOZEN, Hubert, Jan, Jozef et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
15 June 2000 (15.06.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
-----------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0/98414 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/09053	International filing date (day/month/year) 18/11/1999	Priority date (day/month/year) 20/11/1998
International Patent Classification (IPC) or national classification and IPC C07J1/00		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 15/06/2000	Date of completion of this report 10.11.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rudolf, M Telephone No. +49 89 2399 8604 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/09053

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

2-14, 14a, 15, 16 as originally filed

1 as received on 29/09/2000 with letter of 29/09/2000

Claims, No.:

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/09053

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims 1-6
	No: Claims
Inventive step (IS)	Yes: Claims 1-6
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-6
	No: Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/09053

To section V:

The following prior art documents have been cited in the search report:

- D1: C. LOBACCARO ET AL: 'Steroidal Affinity Labels of the Estrogen Receptor. 3. Estradiol 11.beta.-n-Alkyl Derivatives Bearing a Terminal Electrophilic Group: Anti-estrogenic and Cytotoxic Properties' JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 14, 4 July 1997 (1997-07-04), pages 2217-2227, XP002100729 WASHINGTON US
- D2: E. NAPOLITANO ET AL: '11.beta.-Substituted Estradiol Derivatives. 2. Potential Carbon-11-and Iodine-Labeled Probes for the Estrogen Receptor' JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 14, 7 July 1995 (1995-07-07), pages 2774-2779, XP002100730 WASHINGTON US cited in the application
- D3: DE 41 32 182 A (SCHERING AG) 25 March 1993 (1993-03-25)
- D4: WO 93 13123 A (ROUSSEL UCLAF) 8 July 1993 (1993-07-08)

D1 discloses steroid compounds which are substituted at position 11 with hydrocarbon groups having linear chain lengths of 2, 4, and 10 carbon atoms and additionally bearing functional groups. D1 teaches that the receptor affinity increases when the ethylene chain was changed to the n-butylene chain (page 2219, right-hand col.). D2 discloses steroids compounds having a substituent with a linear carbon chain length of up to 3 carbon atoms. D3 discloses steroid compounds bearing a pentafluorosulfinylnonyl group (i.e. a 9-carbon atoms chain) at the corresponding position (cf. compound 4e). The steroid skeleton of this compound is however bridged between C14 and C17, thus said compound does not correspond to formula (I) as claimed.

In contrast to the compounds described in D1 and D2, the present claims are directed to steroids of formula (I) bearing at position 11 a linear carbon chain from 5-9 carbon atoms. Such compounds are not disclosed in the prior art, therefore the claimed subject matter is novel.

The applicant demonstrated in comparative tests that compounds with a hydrocarbon group with a chain length of 5 carbon atoms or more at position 11 of the steroid ring

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/09053

exhibit a more differentiated receptor affinity (agonist for ER α , antagonist for ER β) compared with compounds which bear a chain of four carbons or shorter at position 11 and which are agonists for both ER α and ER β (cf. table on page 14 of the description). Such differentiated activity of the claimed compounds is not derivable from the cited prior art, the presence of an inventive step therefore can be acknowledged.

ESTROGENIC ESTRA-1,3,5(10)-TRIENES WITH DIFFERENTIAL EFFECTS ON THE ALPHA AND BETA ESTROGEN RECEPTORS, HAVING A LINEAR HYDROCARBON CHAIN OF FROM 5-9 CARBON ATOMS IN POSITION 11

The invention is in the field of estrogenic compounds of the type based on the
5 molecular structure of estradiol. I.e., compounds having a steroidal skeleton the A-
ring of which is aromatic, and having a free or capped hydroxyl group at carbon atom
No. 3 and at either of carbon atoms Nos. 16 or 17. Estrogenic compounds have a
generally recognised utility in the treatment of estrogen-deficiency related disorders,
such as menopausal complaints, osteoporosis, and in contraception.

10 More precisely, the invention pertains to 11 β -substituted estradiol derivatives. Such
11 β -substituted estradiol derivatives are known from, *inter alia*, Napolitano et al. in
J.Med.Chem. 1995, 38, 2774-2779. From this paper, it can be learned that placing a
substituent at the 11 β -position may improve the binding affinity for the estrogen
15 receptor, provided that said substituent is not too large. E.g., with an ethinyl group at
C₁₁, the binding increases, whereas with the next higher homolog, 1-propinyl, it is
reported that the binding affinity undergoes a marked drop.

The state of the art in the field of estrogen receptor affinity discriminates between two
20 estrogen receptors, denoted ER α and ER β , see Mosselman et al., FEBS Letters 392
(1996) 49-53 as well as EP -A- 0 798 378. Since these receptors have a different
distribution in human tissue, the finding of compounds which possess a selective
affinity for either of the two is an important technical progress, making it possible to
provide a more selective treatment of estrogen-deficiency related disorders, with a
25 lower burden of estrogen-related side-effects.

The present invention is based on the unexpected finding that, despite the above
teaching, certain 11 β -substituted estradiol derivatives that deviate from those reported
by Napolitano et al. possess a surprisingly higher estrogen receptor-affinity.
30 Moreover, the present invention pertains to such 11 β -substituted estradiol derivatives

Copy

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0/98414 WO	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 99/ 09053	International filing date (day/month/year) 18/11/1999	(Earliest) Priority Date (day/month/year) 20/11/1998
Applicant AKZO NOBEL N.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

ESTROGENIC ESTRA-1,3,5(10)-TRIENES WITH DIFFERENTIAL EFFECTS ON THE ALPHA AND BETA ESTROGEN RECEPTORS, HAVING A LINEAR HYDROCARBON CHAIN OF FROM 5-9 CARBON ATOMS IN POSITION 11

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

P 99/09053

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07J1/00 A61K31/565 C07J21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C. LOBACCARO ET AL: "Steroidal Affinity Labels of the Estrogen Receptor. 3. Estradiol 11.beta.-n-Alkyl Derivatives Bearing a Terminal Electrophilic Group: Anti-estrogenic and Cytotoxic Properties" JOURNAL OF MEDICINAL CHEMISTRY., vol. 40, no. 14, 4 July 1997 (1997-07-04), pages 2217-2227, XP002100729 WASHINGTON US * page 2218, compound 5b * page 2219; table 1 page 2221; table 2 --- -/--	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

30 March 2000

Date of mailing of the international search report

10/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Watchorn, P.

INTERNATIONAL SEARCH REPORT

International Application No.

P 99/09053

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. NAPOLITANO ET AL: "11.beta.-Substituted Estradiol Derivatives. 2. Potential Carbon-11-and Iodine-Labeled Probes for the Estrogen Receptor" JOURNAL OF MEDICINAL CHEMISTRY., vol. 38, no. 14, 7 July 1995 (1995-07-07), pages 2774-2779, XP002100730 WASHINGTON US cited in the application page 2776; table 1	1-6
A	DE 41 32 182 A (SCHERING AG) 25 March 1993 (1993-03-25) the whole document	1-6
A	W0 93 13123 A (ROUSSEL UCLAF) 8 July 1993 (1993-07-08) * the whole document, in particular, page 17, paragraph 3-4 *	1-6